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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/636,243	WANG ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,6 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-6, 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Prosecution on the merits of this application is reopened in view of the suggestion of the Board in the decision rendered on 5/30/07 and applicants amending the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-6 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pomerantz in view of Krylov [or Marmostein] for the reasons stated in the decision rendered by the Board of Patent Appeals on 5/30/07 and reiterated below.

The Pomerantz publication has been described for its disclosure of a zinc finger fused to the naturally occurring dimerization domain extracted from the GAL4 protein. Pomerantz's fusion protein differs from the fusion protein contained in the zinc finger complex of claim 5 by having a naturally occurring dimerization domain, instead Pomerantz points the skilled artisan directly to prior art publications that teach modified

dimerization domains. Such domains are non-naturally occurring and "join each other by specific binding," meeting the requirements of the claimed "peptide linkers." See claim 5. In particular, reference 19 (hereinafter"Krylov"), cited by Pomerantz for its studies of the coiled-coil interaction motif, describes "protein design rules that can be used to modify leucine zipper-containing proteins to possess novel dimerization properties." Krylov, page 2850, column 1. "33 different leucine zipper proteins containing 27 different systematic combinations of amino acids" were produced. Id., page 2856, column 2 ("Discussion"). See also Fig. 1B for a list of exemplary "mutant proteins." Id., page 2850, column 2. The mutant proteins were mixed together under conditions which facilitated dimer formation. By measuring the stability of the dimers formed (id., page 2852-53, "Thermodynamic stability"), Krylov was able to demonstrate that certain modified dimers had increased stability and specificity as compared to the unmodified form. ("Novel heteroloqous interactions regulate dimerization specificity .... In the second mixing experiment, the stability of the heterodimer is calculated to be greater than the average of the two homodimer stabilities, thus favoring the formation of heterodimers." Id., page 2856, columns 1-2.) Thus, the element missing from Pomerantz - non-naturally occurring peptide linkers

- is supplied by Krylov. The skilled worker would have had a reasonable expectation that Krylov's domains could be utilized to complex zinc fingers to which they are attached in view of Krylov's success in not only modifying their binding activity, but in making it stronger (i.e., more stable). Krylov also teaches dimerization domains having the same sequence, meeting the limitations of clam 6. See e.g., id., page 2856, column 1, describing homo- and heterodimers, where the homodimers have "the same sequence." Pomerantz describes dimers between ZFGD1 fusion protein, where each fusion contains the same zinc finger. Pomerantz, Abstract ("a dimeric zinc finger protein, ZFGDI"). This meets the requirements of claim 20. In sum, we find that Pomerantz and Krylov disclose all elements of the subject matter recited in claims 5, 6, and 20. For the reasons discussed above, the skilled worker would have considered these claims obvious in view of Pomerantz's express suggestion to combine its teaching with Krylov (i.e., reference 19), and Krylov's disclosure that would have led the skilled worker to reasonably expect that the combination would work.

Response to Arguments

Pomerantz was cited for disclosing a zinc finger protein fused to a naturally occurring dimerization domain extracted from the GAL4 protein and for suggesting the use, including

citation of various references, of non-naturally occurring dimerization domains. Id. Krylov, reference 19 of Pomerantz, was cited for demonstrating that non-naturally occurring peptide linkers could be utilized to complex zinc fingers, ld. In view of the foregoing amendments and following remarks, Applicants submit that the claims are non-obvious over the cited references. The Supreme Court in KSR lnt 'l Co. v. Teleflex, Inc., No 04-1350 (U.S. Apr. 30, 2007) reaffirmed the viability of the four factual inquiries underlying an obviousness analysis provided in Graham v. John Deere, 148 USPQ 459, 467 (U.S. 1966). These factors include: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary considerations. Moreover, the Supreme Court in KSR recognized that the "teaching, suggestion, or motivation" analysis provides a helpful insight in determining whether the claimed subject matter is obvious. This analysis is provided in MPEP § 2142. In particular, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success.

Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. As noted by the Board in their Decision on Appeal, the teaching or suggestion to make the claimed combination, as well as the reasonable expectation of success, must be found in the prior art, not in applicant's disclosure. See, e.g., In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991), also cited on page 13 of the Board's Decision on Appeal. In view of the law regarding obviousness, Applicants respectfully submit the claims as pending are not obvious over Pomerantz and Krylov.

In reply, the Board has correctly applied the Graham v. John Deere determination as thoroughly discussed above. Furthermore, the court in KSR ruled that:

> The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation……. The diversity of inventive pursuits and of modern technology counsels against **limiting the analysis** in this way….. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility. (Emphasis added).

Applicants argue that Krylov is completely silent as to zinc finger proteins, disclosing only leucine zipper and helix loop helix proteins. As was known in the art at the time of filing and noted throughout the specification, zinc finger

proteins (as claimed) do not contain leucine zipper or HLH motifs characteristic of the proteins as disclosed in Kylov. See, e.g. Section II of the specification starting at page 14, line 11.

In reply, Krylov is employed not for the purpose as argued. Rather, for its teachings that a non-naturally occurring linker as GAL can be used to dimerize or link two fusion proteins. Furthermore, the Board did not preclude the other linkers given by Pomerantz throughout the article, (for example, the Marmostein reference is also cited by Pomerantz, which discloses the DNA binding zinc finger protein). Pomerantz teaches fusion finger proteins except, as stated by the Board, for the linker that fuses the two zinc finger proteins. The linkers are expressly articulated by Pomerantz as all being known in the art to dimerize fusion proteins. The Board has not only applied the Graham v. Deere test but also provided the motivation and expectation of success why one having ordinary skill in the art would use a non-natural linker as taught by **e.g.**, Krylov in the fusion proteins of Pomerantz.

Applicants state that unlike the claimed complexes in which each component of the fusion protein comprises a zinc finger protein that binds to DNA in a sequence-specific manner, Pomerantz explicitly teaches that the GAL4 element does not bind

to DNA in a sequence-specific manner (see, page 967, right column of Pomerantz, emphasis added):

> The utility of this zinc finger-GAL4 fusion rests on the expectation that specificity will be determined primarily by the zinc fingers, which can be designed or selected to recognize desired target sites. **Although the GAL4 linker and dimerization element contact DNA, they do not make any base-specific contacts in the crystal structure** (18). Binding studies with ZFGD1 confirmed that the central 13 base-pair region of this site, ***where the GAL4 linker and dimerization elements are expected to contact the DNA (Figure 1), makes little contribution to sequence-specific recognition.***

In reply, attention is drawn to Pomerantz at page 966, col. 1 which states:

> In this paper, we report the design and characterization of the zinc finger-GAL4 fusion. We find that our **designed protein-binds the predicted DNA sequence as a dimer and that its sequence specificity is primarily determined by the zinc fingers.** • We also show that novel zinc fingers; selected by phage display, can readily be incorporated into this design. In principle, this strategy allows almost any sequence to be targeted through heterodimeric recognition of asymmetric binding sites. (Emphasis added).

Furthermore, the claims do not also recite that the linker binds to the DNA in a sequence-specific manner. As well known in the art and taught by Pomerantz the binding to DNA sequence is primarily determined by the zinc finger**s**. It is immaterial as to whether little contact is made. Obviousness does not require absolute predictability.

Applicants argue that Pomerantz clearly indicates that GAL4 was fused to a zinc finger protein in order to enhance the affinity and specificity of its fusion zinc finger protein partner (page 966, left column of Pomerantz, emphasis added):

> The GAL4 domain was chosen because structural information is available for this domain (18) and because it contains a coiled-coil motif, **a simple**, well- understood structure that can be further modified for design purposes. **The GAL4 dimerization motif is also interesting because it docks to DNA and presumably would help to position and orient the fused zinc finger domains. Moreover, the dimerization motif does not appear to require specific sequences for binding.**

Thus, Pomerantz teaches away from complexes as claimed comprising two zinc finger proteins that each bind to DNA in a sequence-specific manner and wherein the zinc finger proteins are linked by a non-naturally occurring peptide. Pomerantz clearly chose not to form fusions of zinc finger proteins because their binding to their target sites was specific and because using two sequence-specific binding zinc finger proteins as claimed would not be a "simple" structure like Pomerantz's fusions containing the GAL4 dimerization domain. (See, passage of Pomerantz reproduced above). Therefore, there is no motivation in Pomerantz or Krylov, or any combination of Pomerantz and Krylov to form complexes of two zinc finger proteins, each zinc finger protein binding specifically to DNA and linked via a non-naturally occurring peptide linker. When

the references are considered as a whole for what they fairly teach, there are several elements missing from the combination. As stated in KSR, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, page 14. Here, as explained above, less than all of the elements are set forth in the stated combination and, moreover, the primary reference teaches away from complexes of DNA-binding zinc finger proteins linked by non-naturally occurring linkers.

In reply, simply because Pomerantz studied that a dimerization **motif** is not where the binding occurs does not in any way indicates a teaching away. Rather, as positively taught by Pomerantz binding occurs primarily in the zinc finger protein i.e., in the other residues, besides the studied motif of the zinc finger protein. Nonetheless, the claims do not also preclude a motif for its binding to DNA.

Pomerantz does not disclose each of the claimed elements separately then combining them. Rather, as a single, collective entity or aggregate of two fusion proteins combined by a dimerization linker wherein the dimerization linker, is expressly and positively recited as GAL. Pomerantz therefore expressly and clearly discloses the complex of a zinc finger protein with a linker as GAL dimer.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 5 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Barbas et al (USP 6242568) or Eisenberg et al (6453242).

Barbas et al discloses at e.g., col. 28, line 25 up to col. 29, line 51:

....Zinc finger proteins containing from about 2 to 20 zinc fingers Zif(2) to Zif(20), and preferably from about 2 to 12 zinc fingers, may be fused to the leucine zipper domains of the Jun/Fos proteins, prototypical members of the bZIP family of proteins (O'Shea, et al., Science, 254:539, 1991). Alternatively, zinc finger proteins can be fused to other proteins which are capable of forming heterodimers and contain **dimerization domains. Such proteins will be known to those of skill in the art.**
The Jun/Fos leucine zippers are described for illustrative purposes and preferentially form heterodimers and allow for the recognition of 12 to 72 base pairs. Henceforth, Jun/Fos refer to the leucine zipper domains of these proteins. Zinc finger proteins are fused to Jun, and independently to Fos by methods commonly used in the art to link proteins. Following purification, the Zif-Jun and Zif-Fos constructs (SEQ ID NOS: 33, 34 and 35, 36 respectively), the proteins are mixed to spontaneously form a Zif-Jun/Zif-Fos heterodimer. Alternatively, coexpression of the genes encoding these proteins results in the formation of Zif-Jun/Zif-Fos heterodimers in vivo. Fusion of the heterodimer with an N-terminal nuclear localization signal allows for targeting of expression to the nucleus (Calderon, et al, Cell, 41:499, 1982). Activation domains may also be incorporated into one or each of the leucine zipper fusion constructs to produce activators of transcription (Sadowski, et al., Gene, 118:137, 1992). These dimeric constructs then allow for specific activation or repression of transcription. ***These heterodimeric Zif constructs are advantageous since they allow for recognition of palindromic sequences (if the fingers on both Jun and Fos recognize the same DNA/RNA sequence) or extended asymmetric sequences (if the fingers on Jun and Fos recognize different DNA/RNA sequences).***

As recognized by the Zif268-Fos/Zif268 Jun dimer (x is any number). The spacing between subsites is determined by the site of fusion of Zif with the Jun or Fos zipper domains and the length of the linker between the Zif and zipper domains. Subsite spacing is determined by a binding site selection method as is common to those skilled in the art (Thiesen, et al., Nucleic Acids Research, 18:3203, 1990). Example of the recognition of an extended asymmetric sequence is shown by Zif(C7).sub.6 -Jun/Zif-268-Fos dimer. This protein consists of 6 fingers of the C7 type (EXAMPLE 11) linked to Jun and three fingers of Zif268 linked to Fos, and **recognizes the extended sequence**.... (All emphasis added.)

Eisenberg et al discloses at e.g., col. 9, line 48 up to col.10, line 60:

Zinc finger proteins are formed from zinc finger components. For example, zinc finger proteins can have one to thirty-seven fingers, commonly having 2, 3, 4, 5 or 6 fingers. ***A zinc finger protein recognizes and binds to a target site (sometimes referred to as a target segment) that represents a relatively small subsequence within a target gene. Each component finger of a zinc finger protein can bind to***

a subsite within the target site. The subsite includes a triplet of three contiguous bases all on the same strand (sometimes referred to as the target strand). The subsite may or may not also include a fourth base on the opposite strand that is the complement of the base immediately 3' of the three contiguous bases on the target strand. In many zinc finger proteins, a zinc finger binds to its triplet subsite substantially independently of other fingers in the same zinc finger protein. Accordingly, the binding specificity of zinc finger protein containing multiple fingers is usually approximately the aggregate of the specificities of its component fingers. For example, if a zinc finger protein is formed from first, second and third fingers that individually bind to triplets XXX, YYY, and ZZZ, the binding specificity of the zinc finger protein is 3'XXX YYY ZZZ5'.

The relative order of fingers in a zinc finger protein from N-terminal to C-terminal determines the relative order of triplets in the 3' to 5' direction in the target. For example, if a zinc finger protein comprises from N-terminal to C-terminal the first, second and third fingers mentioned above, then the zinc finger protein binds to the target segment 3'XXXYYYZZZ5'. If the zinc finger protein comprises the fingers in another order, for example, second finger, first finger, third finger, then the zinc finger protein binds to a target segment comprising a different permutation of triplets, in this example, 3'YYYXXXZZZ5' (see Berg & Shi, Science 271, 1081-1086 (1996)). The assessment of binding properties of a zinc finger protein as the aggregate of its component fingers is, however, only approximate, due to context-dependent interactions of multiple fingers binding in the same protein.

Two or more zinc finger proteins can be linked to have a target specificity that is the aggregate of that of the component zinc finger proteins (see e.g., Kim & Pabo, PNAS 95, 2812-2817 (1998)). For example, a first zinc finger protein having first, second and third component fingers that respectively bind to XXX, YYY and ZZZ can be linked to a second zinc finger protein having first, second and third component fingers with binding specificities, AAA, BBB and CCC. The binding specificity of the combined first and second proteins is thus 3'XXXYYYZZZ_AAABBBCCC5', where the underline indicates a short intervening region (typically 0-5 bases of any type). In this situation, the target site can be viewed as comprising two target segments separated by an intervening segment.

Linkage can be accomplished using any of the following peptide linkers. TGE KP (SEQ ID NO:2) (Liu et al., 1997, supra.); (G.sub.4 S).sub.n (SEQ ID NO:3) (Kim et al., PNAS 93, 1156-1160 (1996.); GGRRGGGS (SEQ ID NO:4); LRQRDGERP (SEQ ID NO:5); LRQKDGGGSERP (SEQ ID NO:6) ; LRQKD(G.sub.3 S).sub.2 ERP (SEQ ID NO:7). Alternatively, flexible linkers can be rationally designed using computer program capable of modeling both DNA-binding sites and the peptides themselves or by phage display methods. In a farther variation, noncovalent linkage can be achieved by fusing two zinc finger proteins with domains promoting

heterodimer formation of the two zinc finger proteins. For example, one zinc finger protein can be fused with **fos and the other with jun...**

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Cox et al (6534261) teaches a synthetic linker as PEG that links ZFPs.

2. Kim et al (USP 6479626) discloses linkers that fuse two DNA binding domains of a chimeric zinc finger protein.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571 272-0763. The fax phone number for the organization where this application or proceeding isassigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TDW

T. D. Wessendorf
Primary Examiner
Art Unit 1639

9/27/07